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Original Research Article—*Special issue: Atrial Fibrillation*

Poor relationship between left atrial diameter and volume in patients with atrial fibrillation

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ABSTRACT

Background: Left atrial (LA) enlargement is a predictor of worse outcome after catheter ablation for atrial fibrillation (AF). We investigated the correspondence between single LA diameter (LAd) and LA volume (LAV) in patients undergoing catheter ablation for AF.

Methods: Total 782 patients (aged 58 ± 11 yrs; 70% males; 56% paroxysmal AF) were enroled in 2 centres in the period of 2007–2011. Echocardiographic antero-posterior LAd was assessed in parasternal long-axis view and LAV was derived from electroanatomic 3 D reconstruction of LA (183 ± 50 CARTO mapping points; 55% CT image registration).

Results: Mean LAd was 45 ± 6 mm (median: 45; IQR: 41–49; range: 25–73 mm) and mean LAV was 134 ± 42 ml (median: 128; IQR: 103–160; range: 46–313 ml). Correlation between both variables was weak ($r = 0.56$; $p < 0.0001$) and area under the ROC curve for the LAd-based prediction of LAV > 130 was 0.76. Accordingly, severe dilation of LA (LAV > 160 ml; upper quartile) was found only in 56% of patients with LAd > 50 mm while it appeared in 11% of those with LAd < 45 mm. In multivariate regression analysis, age, gender, and type of AF were independent covariates of LAV yielding the equation of LAV (ml) $= 68 + 0.41$.cube LAd (cc)$+15$ (if male)$+0.48$.-age (yrs) $- 21$ (if paroxysmal AF). Substantial between-centre bias was also found reflecting subjective nature of echocardiographic readings. Adjustment for all covariates improved the correspondence between LAd-predicted and true LAV only modestly (AUC increased from 0.76 to 0.83) with wide 95% limits of agreement (-58 to $+60$ ml).

Conclusions: Considerable disagreement between echocardiographic LAd and 3D mapping LAV was observed in patients with non-valvular atrial fibrillation. Single LA dimension should not be

Abbreviations: RFCA, radiofrequency catheter ablation; LA, left atrium; LAd, left atrial diameter; LAV, left atrial volume; AF, atrial fibrillation; PV, pulmonary vein; PLAX, parasternal long axis view; SHD, structural heart disease; AH, arterial hypertension; DM, diabetes mellitus; CT, computer tomography; MR, magnetic resonance; IQR, interquartile range; ROC, receiver operating characteristics; AUC, area under the curve

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considered relevant criterion for the indication of rhythm/rate control therapy and, particularly, for the selection of suitable candidates for catheter ablation.

1. Introduction

Radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) is now established therapy in selected patients [1]. Assessment of left atrial (LA) size, which has been identified as a predictor of RFCA efficacy [2–9], is essential when ablation treatment for AF is considered.

Echocardiography is widely available non-invasive imaging technique for the assessment of LA size [10]. Multiple 2D echo indices of LA volume (LAV) were mutually compared as well as correlated with computer tomography (CT) or magnetic resonance (MR) imaging [11–14]. Real time 3D echocardiography was recently introduced and validated for the measurement of LAV [15–19].

Despite these advances in quantification of LA anatomy, the simplest index, antero-posterior LA diameter (LAd) assessed from long-axis parasternal (PLAX) view, was predominantly used for stratification of risk for AF recurrence in numerous RFCA studies as reflected by recent metaanalysis [20]. It has long been known, however, that LAd poorly correlates with LAV [21–24]. During the RFCA procedure, electro-anatomic 3-D reconstruction of the LA can be accurately performed [25] and LAV can be assessed without geometric assumptions [26,27].

Little is known about factors that may influence the relationship between LAd and LAV. Our retrospective study aimed at investigating this relation in multivariate fashion in patients undergoing RFCA for AF in whom detailed LA electroanatomic mapping was available and considered as gold standard for LAV assessment.

2. Methods

Consecutive patients, who underwent RFCA for AF at two cardiocentres between May 2007 and December 2011, were analysed. The data were retrieved from dedicated registry that was shared by both centres (2nd Department of Internal Medicine—Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague and Department of Cardiology, Heart Centre, Hospital Podlesí, Třinec). Collection of data was approved by the local ethics committees of both institutions. All patients gave an informed consent with procedure.

LA mapping was performed in standardized way prior to ablation procedure. Three-dimensional electroanatomic mapping system (CARTO XP or CARTO 3, Biosense-Webster Inc., Diamond Bar, CA, USA) and manual catheter navigation was used for the reconstruction of the LA endocardial surface. Uniformly distributed mapping points were acquired at sites with stable endocardial contact. Special attention was played not to acquire the mapping points behind the pulmonary vein ostia. Orifice and proximal part of left atrial appendage was always mapped. Precise delineation of mitral annulus was performed in all cases. Intracardiac echocardiography was used to visualise and tag the critical structures. A 3-D virtual shell of LA was built by software interpolations over the co-ordinates of multiple endocardial points. When multi-detector computed tomography reconstruction of LA was available, the CT image was registered to CARTO map by automatic algorithm that minimises the distance between the mapping points and the surface of CT image. Merged display of CT image and electroanatomic map was used to eliminate incidental internalised and/or externalised mapping points in order to improve the quality of registration. Finally, LAV was assessed using a built-in computation function of the Biosense system. Patients with <50 mapping points were excluded from the analysis.

Echocardiographic examinations were performed according to the recommendations of American Society of Echocardiography [10]. All echocardiograms were acquired before RFCA and in majority of patients within 24 h before the procedure. LAd was defined as end-systolic, M-mode derived antero-posterior linear dimension in PLAX view using 2-D guidance for the positioning of cursor.

2.1. *Statistical analysis*

Continuous variables were expressed as means with standard deviations and compared by the 2-tailed *t*-test for independent samples. Categorical variables were expressed as percentages and compared by χ^2-test. Pearson's correlation and multivariate linear regression were used to analyse the relationship between LAd together with other clinical covariates as dependent variables and true LAV as independent variable. Cubed LAd entered the regression model in order to linearise its relation to LAV. Multivariate equation for LAV prediction was obtained by stepwise forward model and the agreement between measured and predicted LAVs was analysed using the method of Bland and Altman. Receiver operating characteristics for LAd (or predicted LAV) vs. above-median CARTO-derived LAV were assessed. *P*-value<0.05 was considered significant. All analyses were performed using the STATISTICA vers.6.1 software (Statsoft, Inc., Tulsa, USA).

3. Results

Data from 782 patients (aged 58 ± 11 years; 70% males; 56% paroxysmal AF) were included to the analysis. Baseline characteristics of total population and subgroups by type of AF are shown in Table 1. Males were significantly younger than females (57 ± 9 vs. 62 ± 8 years, $p<0.0001$). Mean LAd was 45 ± 6 mm (median: 45; interquartile range [IQR]: 41–49; range: 25–73 mm) and mean LAV was 134±42 ml (median: 128; IQR: 103–160; range: 46–313 ml). The distributions of LAd and LAV are illustrated in Fig. 1.

Pearson's correlation coefficient between cubed LAd and LAV was 0.56; $p<0.0001$ (Fig. 2). The correlation was significantly weaker in females and in patients who were investigated in one of participating centres (Table 2). Positive and negative predictive characteristics of LAd for LAV at two cut-off values of >45 and >50 mm, and >130 ml and >160 ml, which represent approximately medians and upper quartiles, respectively, are shown in Table 3. This indicates that severe dilation of LA (LAV >160 ml) was found only in 56% of patients with LAd >50 mm while it appeared in 11% of those with LAd <45 mm.

Apart from LAd, age, gender, type of AF, and centre were significantly associated with LAV by multivariate regression analysis, while the presence of structural heart disease, hypertension, diabetes, and CT registration were not independent

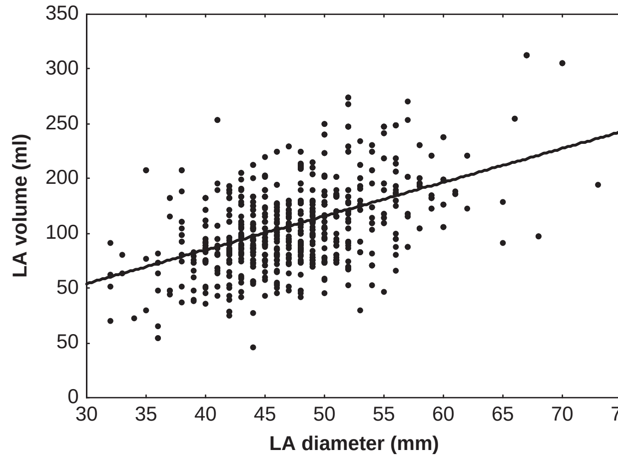

Fig. 2 – Correlation between left atrial diameter and left atrial volume. LA—left atrium.

Table 1 – Baseline characteristics.

	Total population ($n=782$)	Paroxysmal AF ($n=435$)	Non-paroxysmal AF ($n=347$)
Age (years)	58±11	58±10	59±9
Males	546 (70%)	282 (65%)	264 (76%)†
Arterial hypertension	465 (59%)	241 (55%)	224 (65%)†
Diabetes mellitus	107 (14%)	57 (13%)	50 (14%)
Structural heart disease	80 (10%)	29 (7%)	51 (15%)†
Coronary artery disease	54 (6.9%)	26 (6%)	28 (8%)
ECHO LAd (mm)	45±6	43±6	47±6
CARTO mapping points	183±50	173±44	195±52†
CT image registration	431 (55%)	254 (58%)	177 (51%)
CARTO-derived LAV (ml)	134±42	119±33	153±43

AF—atrial fibrillation; CT—computer tomography; LAd—antero-posterior left atrial diameter; LAV—left atrial volume. Values represent mean±standard deviation or number (percentage).
† $p<0.05$ (Paroxysmal AF vs. Non-paroxysmal AF).

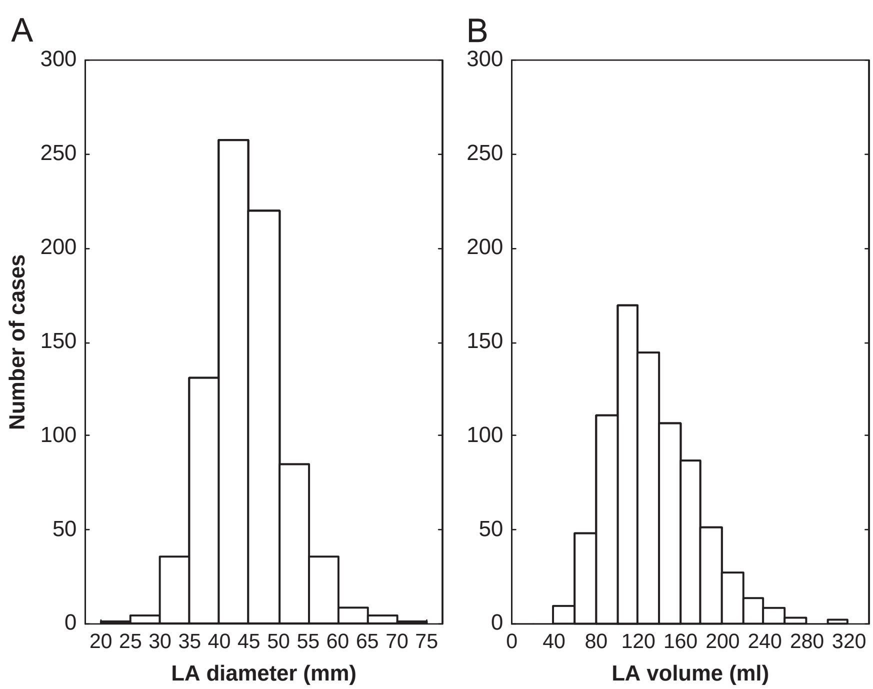

Fig. 1 – Distribution of left atrial diameter and volume. LA—left atrium.

Table 2 – Pearson's correlation between cube LAd and LAV in specific clinical categories.

Category 1	N_1	R_1	Category 2	N_2	R_2	p-value (R_1 vs. R_2)
Enroling centre A	560	0.52	Enroling centre B	222	0.72	<0.0001
Age >60 years	352	0.51	Age ≤60 years	430	0.59	NS
Male gender	546	0.56	Female gender	236	0.41	0.01
Paroxysmal AF	435	0.48	Non-paroxysmal AF	347	0.53	NS
SHD present	80	0.65	SHD absent	702	0.55	NS
AH present	465	0.52	AH absent	317	0.60	NS
DM present	107	0.42	DM absent	675	0.58	NS
CT image registration YES	431	0.58	CT image registration NO	351	0.52	NS

AF—atrial fibrillation; AH—arterial hypertension; CT—computer tomography; DM—diabetes mellitus; LAd—antero-posterior left atrial diameter; LAV—left atrial volume; SHD—structural heart disease; N_1, N_2—number of patients; R_1, R_2—correlation coefficients.

Table 3 – Positive and negative predictive values of LAd for LAV.

	LAV > 130 ml		LAV > 160 ml	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)
LAd > 45 mm	67	68	41	89
LAd > 50 mm	80	58	56	82

LAd—antero-posterior left atrial diameter; LAV—left atrial volume; NPV—negative predictive value; PPV—positive predictive value.

covariates. Detailed results are shown in Tables 4 and 5. Generally, LAV could be estimated by the equation: LAV (ml)=68+0.41.LAd^3 (cm^3)+15 (if male)+0.48.age (yrs) – 21 (if paroxysmal AF).

Despite the adjustment for covariates, absolute and relative differences between CARTO-derived and LAd-predicted LAV ranged from −100 to +113 ml and from −68% to +114%, respectively, with standard deviation of 31 ml (coefficient of variation of 23%). We found wide 95% limits of agreement (−58 to +60 ml) between true and predicted LAV (Fig. 3). The relative error in LAV prediction was >10%, >20%, and >30% in 64%, 35%, and 13% of patients, respectively. Poor ability of LAd alone to predict true LAV >130 ml, as demonstrated by receiver operating characteristics (ROC) with area under the curve (AUC) of 0.76, improved only modest (AUC=0.83) after adjustment for significant covariates (Fig. 4). Fig. 5 shows between-centres difference in ROC curves with AUC of 0.76 vs. 0.81.

4. Discussion

The study showed substantial disagreement between echocardiographic LAd and LAV assessed by 3D electroanatomic mapping in patients with non-valvular atrial fibrillation. Considerably large population, which was satisfactorily balanced in terms of gender and type of AF and had wide range of LA size, enabled comprehensive analysis of factors that are responsible for this disagreement. Because the data were collected in 2 centres, the effect of deviation from presumably standardized measurement techniques could also be indirectly assessed.

It was shown that age, gender and type of AF had significant and independent impact on the relationship between LAd and LAV. Single echocardiographic diameter may overestimate the LAV in younger patients, in females, and in patients with paroxysmal AF. The opposite may be true for older patients, males, and those with persistent AF. By adjusting for these covariates, the predictive characteristics of LAd for LAV improved but still remained far from the optimum.

The disagreement between LAd and LAV is not a novel observation. M-mode LAd was correlated to biplane ECHO LAV (r=0.76) [21], to 3D ECHO LAV (r=0.78) [23], and to LAV assessed by ellipsoidal formula in large Olmsted County Population Study (kappa=0.53) [22]. In patients with AF, even poorer correlation (r=0.49) was reported between LAd and CT-assessed LAV, probably because of greater variability of atrial anatomy in this population of patients referred for catheter ablation [24].

Although LAd is inaccurate for the assessment of LA size, it is widely available measure (sometimes the only reported index) in clinical registries or even in prospective clinical trials. That is why any information on the relationship between LAd and LAV, which was investigated in our study, may be of practical value.

LA enlargement assessed by LAd was predictive of risk for nonvalvular AF in Framingham Heart Study [28]. Numerous studies reported predictive value of LAd for clinical success of RFCA [20]. Only recently, several studies reported LAV assessed by echocardiography [3,8], CT imaging [4–6] and MR imaging [7,9] to be associated with clinical outcome. Direct comparison of predictive power of LAd versus LAV for arrhythmia-free survival in patients after RFCA is missing. There is only single report on superiority of LAV to LAd in the prediction of AF recurrence after successful electrical cardioversion [29]. In patients with sinus rhythm, LAV was a more robust marker of cardiovascular events than LAd [30].

We assumed CARTO-derived LAV, which can accurately be assessed irrespective of anatomical LA abnormalities, to be a golden LAV standard. This assumption was not solely based on our own experience with this imaging modality. Other report demonstrated high correspondence between LA CARTO map and CT-assessed LA anatomy [25]. LAV assessment by the electroanatomic mapping has already been used in 2 small studies and showed reasonable agreement with LAV assessed either by biplane 2D echocardiography [26] or 3 D echocardiography [27]. In our study, high-density electroanatomic maps were created by experienced operators. In more than half of procedures, CT image registration was

Table 4 – Multivariate determinants of CARTO-derived LAV.

Parameter	B statistics	95% CI	P value
Intercept	54.7	37.6–71.8	< 0.0001
Ablation centre (A=1; B=0)	20.8	15.8–25.9	< 0.0001
Male gender (no=0; yes=1)	12.4	7.1–17.6	< 0.0001
Age (years)	0.42	0.2–0.7	0.002
Paroxysmal AF (no=0; yes=1)	−19.7	−24.4 to 15.1	< 0.0001
CT image registration (no=0; yes=1)	1.8	−2.7 to 6.4	NS
Arterial hypertension (no=0; yes=1)	1.0	−3.8 to 5.9	NS
Diabetes mellitus (no=0; yes=1)	−5.0	−11.7 to 1.7	NS
Structural heart disease (no=0; yes=1)	4.7	−2.6 to 12.0	NS
Cube LAd (cm^3)	0.42	0.4–0.5	< 0.0001

AF—atrial fibrillation; CT—computer tomography; LAd—antero-posterior left atrial diameter; LAV—left atrial volume.

Table 5 – Stepwise forward regression analysis for LAV as dependent variable.

	Model 1		Model 2	
Parameter	B statistics	P value	B statistics	P value
Intercept	56.2	< 0.0001	67.8	< 0.0001
Ablation centre (A=1; B=0)	20.3	< 0.0001	–	–
Male gender (no=0; yes=1)	12.7	< 0.0001	14.7	< 0.0001
Age (years)	0.42	0.001	0.48	0.001
Paroxysmal AF (no=0; yes=1)	−20.0	< 0.0001	−21.4	< 0.0001
Cube LAd (cm^3)	0.42	< 0.0001	0.41	< 0.0001

AF—atrial fibrillation; LAd—antero-posterior left atrial diameter; LAV—left atrial volume. Ablation centre information is excluded from the Model 2 in order to obtain generally applicable regression equation.

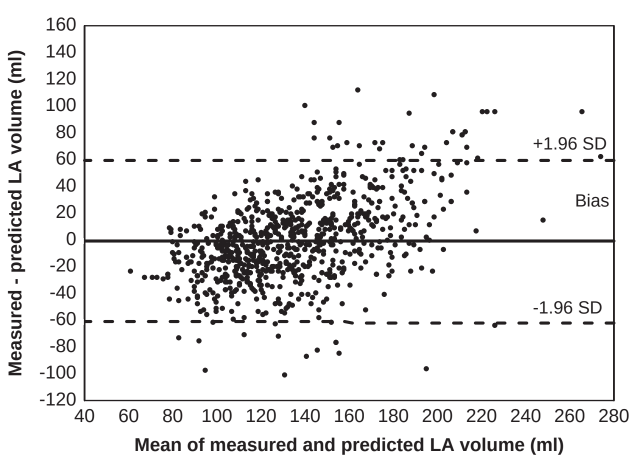

Fig. 3 – Agreement between measured (CARTO-derived) and LAd-predicted LAV. Bland–Altman plot with mean difference of 0.9±30 ml and 95% limits of agreement (−58 to +60 ml). LAd—antero-posterior left atrial diameter; LAV—left atrial volume; SD—standard deviation.

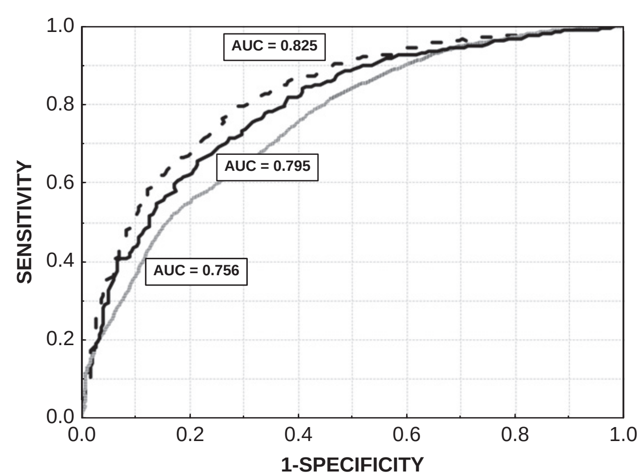

Fig. 4 – Receiver operating characteristics for the prediction of LAV >130 ml—impact of adjustment for covariates. Predictors are as follows: (1) LAd (dotted line), (2) LAV estimated from LAd, age, gender, and type of AF (solid line), and 3) LAV estimated as in (2) with accounting for ablation centre information (dashed line). AUC=area under the curve; LAV—left atrial volume.

performed which invariantly exhibited excellent spacial agreement between CARTO maps and CT images.

Because the LA is a non-spherical cavity, any LA linear dimension cannot reflect accurately true LA size [31]. LA size assessment by echocardiography is not only limited by non-spherical LA anatomy but also by the measurement error associated with single reading compared CARTO-mapping with multiple readings (multiple points) where individual inaccuracies are mutually nullified. Furthermore, echocardiography is patient-dependent (incidentally poor echocardiographic window) and observer-dependent (appropriate angulation and gain adjustment for clear visualisation of the LA endocardium contour) [11,21]. For non-spherical

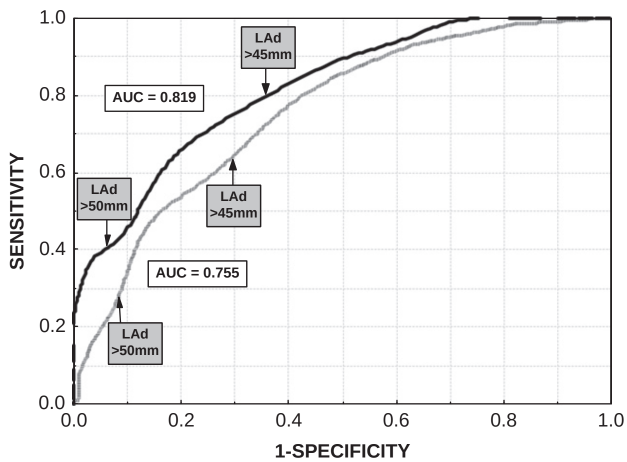

Fig. 5 – Receiver operating characteristics for the prediction of LAV $>$130 ml—impact of centre. Predictive value of LAd for enroling centre A (dotted line) and B (solid line). AUC=area under the curve; LAd—antero-posterior left atrial diameter; LAV—left atrial volume.

chamber, the maximum diameter obtained does not necessarily correspond to anatomically correct projection. It is plausible to speculate that in case of small and/or flattened LA (in young patients, females and patients with paroxysmal AF) echocardiographists are more prone to adjust the projection in order to improve the quality of the image. This is likely a source of LAd and LAV overestimation in such patients as suggested by our multivariate analysis.

For all these reasons, we believe that the disagreement between both methods of LA size assessment is predominantly due to inherent inaccuracy of single echocardiographic LA diameter. Subjective nature of echocardiographic readings is supported not only by considerable bias between centres (significant covariate in multivariate analysis) but also by significant between-centre difference in LAd vs. LAV correlations and, consequently, by dissimilar area under the corresponding ROC curves for diameter vs. volume indices.

4.1. *Study limitations*

The study has several limitations. First, the study was not prospectively designed and the data collection was not independently monitored. Second, both centres did not contributed equally to the enrolment of patients and some dysbalance in patients characteristics also appeared between centres. Third, CT image registration was not performed in all patients in order to minimise the LAV measurement error. Fourth, the incomplete data have not allowed investigating the role of other LA diameters in prediction of LAV. Fifth, the results cannot be extrapolated to other populations, i.e. to patients without AF.

5. Conclusions

The correlation between echocardiographic antero-posterior LAd and CARTO-derived LAV is weak so that LA size can be severely over- or underestimated by the use of single LA diameter. This disagreement can predominantly be attributed to non-spherical LA shape and to within- and between-centres echocardiographic measurement error. Prediction characteristics of LAd for LAV can, to some extent, be improved by the adjustment for significant clinical covariates (gender, age and type of AF). Nevertheless, single LA dimension should not be considered relevant for the indication of rhythm/rate control therapy in patients with AF and, particularly, for the selection of suitable RFCA candidates.

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